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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

MEMORANDUM

TXR NO.: 0053315

DATE: April 20, 2005

SUBJECT: BAS 800 H: Report of the Dose Adequacy Review Team - Dose Selection for a Mouse Carcinogenicity Study

PC Code: 118203; DP Barcode: D316199

FROM: Jessica Kidwell, Executive Secretary Jessica Kidwell
Dose Adequacy Review Team
Health Effects Division (7509C)

THROUGH: Jess Rowland, Chair
Dose Adequacy Review Team
Health Effects Division (7509C)

TO: Joanne Miller, Product Manager
Registration Division (7505C)

Attached please find the DART's recommendations regarding dose selection for a carcinogenicity study in the mouse for BAS 800 H.

Note to Registrant: Please reference this DART memo in the final study as justification for the dose levels selected.

APR 3 0 2005

FINAL REPORT OF THE DOSE ADEQUACY REVIEW TEAM (DART) FINAL

DART Members in Attendance at April 20, 2005 Meeting: (Signature indicates concurrence with the report unless otherwise stated):

Karl Baetcke

Marion Copley

Jessica Kidwell (Executive Secretary)

Jess Rowland

FINAL REPORT OF THE DOSE ADEQUACY REVIEW TEAM (DART) FINAL

BASF submitted a proposal for dose selection for a mouse carcinogenicity study as detailed in the 4/7/05 document entitled "Dose Level Proposal for a Mouse Carcinogenicity Study with BAS 800H." The DART met on April 20, 2005 to discuss this topic.

The Registrant proposed the following doses: Males: 75, 25, 5, 1 ppm
Females: 100, 50, 25, 5 ppm

The DART recommended the following dose levels for the carcinogenicity study in mice based on information from a 28-day study, and more importantly, a 90-day study in mice. [Note: The 28-day and 90-day mouse studies have not yet been formally submitted to or reviewed by the Agency.]

DART recommended doses:

Males: 100, 50, (25, 5) ppm

Rationale: In the 90-day study, severe toxicity in males at 450 ppm manifested as anemia (15% decrease in hemoglobin; 13% decrease in hematocrit), marked elevation of liver enzymes (ALT 793% of control), increased liver weight (134% of control) and liver histopathology (severe/massive diffuse fatty change in the liver, incidence 100%; and lymphoid cell infiltrates, incidence 100%). At the next lower dose of 150 ppm, toxicity was evidenced by anemia (14% decrease in hemoglobin and 11% decrease in hematocrit), elevation of liver enzymes (ALT 292% of control), and liver histopathology (moderate/severe diffuse fatty change in liver, incidence 80%; and lymphoid cell infiltrates, incidence 100%). The anemia severity appears to be unchanged when the 150 ppm dose is compared to the 450 ppm dose for the same time period. However, severity is increased about 5% over time: hematologic parameters were decreased about 10% at 28 days, as compared to about 15 % at 90 days. The 50 ppm dose was considered the NOAEL.

The DART considered a dose of 150 ppm to be too high for the top dose of the carcinogenicity study since the mice may not tolerate it for 18 months. However, the committee considered 75 ppm to be too low based on the magnitude of the effect at 150 ppm. Therefore, the DART recommends a top dose of 100 ppm, which should be sufficiently tolerated over 18 months and still present some evidence of toxicity. The DART also recommends that the next dose be one-half the highest dose tested or 50 ppm, which was a NOAEL in the 90-day study. The DART believes that this top dose of 100 ppm should be adequate to assess the carcinogenicity of the compound. However, if no effects occur at 100 ppm in the carcinogenicity study, the study should be acceptable in conjunction with the results of the short term studies (i.e, 28 and 90 days) and the mode of action of this chemical which were the basis for the doses recommended by the DART. On the other hand, if the top dose of 100 ppm (which is higher than the Registrant's proposed dose of 75 ppm) proves to be excessive, the study should be acceptable because the next lower dose (50 ppm) is one-half of the top dose.

The final selection of the lower doses is at the Registrant's discretion.

Females: 150, 75, (25, 5) ppm

Rationale: In the 90-day study,1350 ppm is excessive based on anemia (14% decrease in hemoglobin; 11% decrease in hematocrit), increased liver weight, and histopathological effects in the liver (lymphoid infiltration, 100% incidence) and moderate/severe centrilobular fatty change, 100% incidence). At the next lower dose of 450 ppm, toxicity was evidenced by anemia (4% decrease in hemoglobin; 5% decrease in hematocrit), increased liver weight, and liver histopathology (lymphoid infiltration, 100% incidence; moderate centrilobular fatty change, 80% incidence). Anemia (5% decrease in hemoglobin and hematocrit) and liver histopathology (moderate centrilobular fatty change, 10% incidence) was seen at 150 ppm. The NOAEL was 50 ppm.

The DART recommends a top dose of 150 ppm since no toxicity was seen in the 28-day study and the toxicity in the 90-day study was judged to be adverse but not severe and is consistent with the mode of action of this chemical. The DART believes that this top dose of 150 ppm should be adequate to assess the carcinogenicity of the compound. If the top dose of 150 ppm (which is higher than the Registrant's proposed dose of 100 ppm) proves to be excessive, the study should be acceptable because the next lower dose is one-half of the top dose. The final selection of the lower doses is at the Registrant's discretion.

Note to Registrant for this submission and all future DART submissions: Please submit absolute numbers (including standard deviations) as well as percentages for all data, including body weight, body weight gain, clinical chemistry, and hematology.

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